

determining. Considering the extreme subtleties involved in determining the nature of the rate-limiting step in nonenzymic acyl transfer reactions,²⁰ it is not possible from information concerning aminolysis to predict whether attack or breakdown of a tetrahedral intermediate will be rate determining in the hydrolysis reaction.

Also, we believe that the various factors underlying the efficacy of chymotrypsin catalysis are not necessarily important to the same extent with all substrates and the 115,000-fold difference in the rate of deacylation of acetyltyrosyl²¹ and furoyl-chymotrypsin¹⁰ may not involve equivalent reductions in the effectiveness of all components in the catalytic process. In one of two mechanisms previously proposed to account for the pH dependence of reactions of chymotrypsin with anilides,

(20) (a) S. A. Shain and J. F. Kirsch, *J. Amer. Chem. Soc.*, **90**, 5848 (1968); (b) W. P. Jencks and M. Gilchrist, *ibid.*, **90**, 2622 (1968).

(21) L. W. Cunningham and C. S. Brown, *J. Biol. Chem.*, **221**, 287 (1956).

the pK of the Michaelis complex is presumed to vary with different substrates. This mechanism does not account for the substituent dependence of the rates and is considered unlikely because of difficulties in envisioning a simple mechanism for substrate-induced perturbations in the enzyme pK . The results reported here with furoyl-chymotrypsin indicate that the pK may be perturbed by a process not involving a tetrahedral intermediate. Because of the enormous differences in reactivity of nonspecific and specific substrates we do not feel that this is compelling evidence for rejection of a mechanism involving a tetrahedral intermediate. The dissociation process may be more complex than that given in Scheme II and may reflect a combination of factors such as weak interactions in a Michaelis complex and an acyl-enzyme (Scheme II) and the involvement of a tetrahedral intermediate with an appreciably modified pK (Scheme I and ref 3), and the importance of each of these factors may vary with different substrates.

Diffusion-Controlled and Concerted Base Catalysis in the Decomposition of Hemithioacetals¹

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Abstract: Rate and equilibrium constants are reported for the reactions of benzenethiol, *p*-nitrobenzenethiol, and thioacetic acid with acetaldehyde to form the corresponding hemithioacetals. The hydroxide ion catalyzed breakdown of these hemithioacetals occurs with rate constants near $10^{10} M^{-1} sec^{-1}$ and is largely or entirely limited by the rate of diffusion-controlled encounter of the substrate and catalyst. The energy of activation is 2–3 kcal/mole and the solvent deuterium isotope effect k_{OH^-}/k_{OD^-} is 1.25. In the synthesis reaction, formation of the carbon–sulfur bond and proton transfer (eq 11) occur rapidly and separation of hydroxide ion from the hemithioacetal (eq 10) is the rate-determining step. Weaker bases catalyze the breakdown reaction at a slower rate with a Brønsted slope β of 0.8 ± 0.03 . This indicates that carbon–sulfur bond formation or cleavage and proton transfer are in some sense concerted. Equilibrium constants for hemithioacetal formation are independent of the acidity of the thiol over a range of acidity of 10^7 .

The addition to acetaldehyde of the weakly acidic thiols, ethanethiol, methoxyethanethiol, and methyl mercaptoacetate, to form the corresponding hemithioacetals occurs predominantly through a base-catalyzed pathway, although a general acid catalyzed pathway with a large Brønsted coefficient α becomes significant at low pH values. No general base catalysis has been detected for these reactions and there is no significant water reaction, with the possible exception of the reaction with methyl mercaptoacetate. The observed rate constants for the base-catalyzed reaction with methyl mercaptoacetate indicated that the rate constants for breakdown of the hemithioacetal anion and of proton transfer to this anion are very similar, so that a situation is approached in which a diffusion-controlled proton-transfer step becomes rate determining.² The experi-

ments described here were carried out to test the prediction² that a diffusion-controlled step should become rate determining in the formation and breakdown of hemithioacetals formed from more acidic thiols. As has been reported in a preliminary communication,³ the results confirm the prediction that a diffusion-controlled step is rate determining, but indicate that the proton transfer in these reactions is in some sense concerted with the formation and cleavage of the carbon–sulfur bond (eq 11), rather than a stepwise process.

Experimental Section

Materials. Thioacetic acid and benzenethiol were redistilled under nitrogen before use. *p*-Nitrobenzenethiol was purified by a modification of the procedure of Willgerodt.⁴ Crude thiol (5 g) was dissolved in 25 ml of boiling 5% sodium hydroxide and filtered.

(1) Supported by grants from the National Science Foundation (GB 4648) and the National Institute of Child Health and Human Development of the Public Health Service (HD-01247). R. E. B. was a National Science Foundation Predoctoral Fellow, 1965–1968.

(2) G. E. Leinhard and W. P. Jencks, *J. Amer. Chem. Soc.*, **88**, 3982 (1966).

(3) R. Barnett and W. P. Jencks, *ibid.*, **89**, 5963 (1967).

(4) C. Willgerodt, *Chem. Ber.*, **18**, 331 (1885).

The filtrate was added to excess cold 1 *M* hydrochloric acid. The light yellow precipitate was collected, washed with cold 0.01 *M* hydrochloric acid, dried *in vacuo*, and stored under argon at -10° , mp $78-79^\circ$ (lit.⁴ mp 77°). Acetic acid, methoxyacetic acid, and chloroacetic acid were redistilled. Cyanoacetic acid was recrystallized from 10% ethanol in chloroform. Acetaldehyde was redistilled under nitrogen immediately before use. The mole percent of acid in the redistilled acetaldehyde was generally in the range 0.1-0.3. The ionic strength was maintained at 1.0 *M* with potassium chloride. Distilled water containing 10^{-4} *M* disodium ethylenediaminetetraacetate (EDTA) was used throughout.

Equilibrium Constants. The equilibrium measurements were made at 25.0° using a Zeiss PMQ II spectrophotometer with a thermostated brass block. Teflon-stoppered cuvettes were used throughout. The aldehyde was always present in at least a tenfold excess. The apparent equilibrium constant, K_{app} , for hemithioacetal formation from thioacetic acid and acetaldehyde at pH 2.10 was determined by holding the initial thiol concentration constant and varying the aldehyde concentration. The reaction mixture consisted of 0.02-1.0 *M* acetaldehyde, 0.01 *M* hydrochloric acid, and ca. 1.5×10^{-4} *M* thioacetic acid.

There is no wavelength at which the sole absorbing species is either the thiol or the hemithioacetal. The reaction was followed at 230 $m\mu$, the absorption maximum of the adduct, at which a near-maximal change in absorbance occurs. Equilibration of the reaction mixture occurs in less than 5 sec.

The apparent equilibrium constant for hemithioacetal formation, under conditions in which the aldehyde is present in great excess, is given by eq 1, in which A is the absorption of the equilibrium mixture, A_0 the absorption of thiol alone, A_a the absorption of aldehyde alone, A_∞ the absorption of pure adduct, and a the concentration of total aldehyde and aldehyde hydrate. The values of A_∞ and K_{app} were obtained from the intercepts of plots of the data

$$K_{app} = \frac{[\text{hemithioacetal}]}{[\text{total thiol}][\text{total aldehyde}]} = \frac{(A - A_a - A_0)}{a(A_\infty + A_a - A)} \quad (1)$$

according to eq 2 and 3, respectively. The concentration of total

$$A - A_a = - \frac{(A - A_a - A_0)}{K_{app}a} + A_\infty \quad (2)$$

$$\log a = \log \frac{(A - A_a - A_0)}{(A_\infty + A_a - A)} - \log K_{app} \quad (3)$$

aldehyde and aldehyde hydrate at ionic strength 1.0 *M* was determined spectrophotometrically, based on a molar extinction coefficient of 8.5 for these conditions at 280 $m\mu$.² Because of the similarity of the spectra of thioacetic acid and its hemithioacetal, the equilibrium constant was determined several times to obtain a reliable value.

The apparent equilibrium constant for the formation of the hemithioacetal of benzenethiol and acetaldehyde was determined in the same manner at pH 4.27 by absorption measurements at 236 $m\mu$. The reaction mixture consisted of 0.02 *M* acetate buffer (30% base), ca. 10^{-4} *M* benzenethiol, and 0.02-1.0 *M* acetaldehyde. The apparent equilibrium constant for the formation of the hemithioacetal of *p*-nitrobenzenethiol and acetaldehyde was determined at pH 4.30 by using the absorption of *p*-nitrobenzenethiol anion at 410 $m\mu$ as an indicator of *p*-nitrobenzenethiol concentration. The reaction mixture consisted of 0.04 *M* acetate buffer (30% base), $1.20-1.44 \times 10^{-4}$ *M* *p*-nitrobenzenethiol, and 0.017-0.42 *M* acetaldehyde. Since neither the adduct nor the acetaldehyde absorbs at 410 $m\mu$, K_{app} was determined from plots of the data according to eq 4.

$$\frac{1}{A} = K_{app} \frac{a}{A_0} + \frac{1}{A_0} \quad (4)$$

All solutions for the relatively slow equilibrium and kinetic experiments at low pH were degassed and kept under argon in stoppered cuvettes or test tubes to minimize exposure to oxygen.

Kinetic Measurements. The kinetic measurements were made using a stopped flow device made to fit the thermostated cell compartment of a Gilford 2000 spectrophotometer modified by the addition of capacitors to filter out line voltage noise. The drive syringes were embedded in a thermostated brass block and were

driven with 15-25 lb of nitrogen pressure. The absorbance of the reaction mixture was recorded on a Tektronix 564 storage oscilloscope. The half-life of the reaction was the average of the first and second half-lives, determined directly from the oscilloscope image. The two half-lives were usually within 1-2% of each other. The plastic shield in front of the screen was scored every 2 mm both horizontally and vertically so that accurate half-lives could be determined. Slow reactions were followed with the Gilford chart recorder.

Pseudo-first-order rate constants for the reaction of thioacetic acid with acetaldehyde were usually determined from measurements at 246 $m\mu$, where the thioacetate anion absorbs, but at pH values below about 2.2 the reaction was followed by the appearance of adduct at 230 $m\mu$. Measurements in chloroacetate buffers were made at 253 $m\mu$. The reaction of *p*-nitrobenzenethiol with acetaldehyde was followed by the disappearance of the thiol anion at 410 $m\mu$. With benzenethiol the reaction was followed by the disappearance of thiol at 236 $m\mu$, except in chloroacetate buffers, for which the appearance of adduct was followed at 255 $m\mu$. The reactions were initiated by mixing equal volumes of solutions of ca. 10^{-4} *M* thiol and 0.2 *M* acetaldehyde. The time sweep of the oscilloscope was adjusted so that 2-3 half-lives could be observed. The pH of the reaction mixture was determined by measuring the pH of the effluent from the stopped flow apparatus.

Because of ionization of the thiol, the apparent equilibrium constant, K_{app} , decreases for pH values above the pK_a of the thiol. Hence determination of the rates of hemithioacetal breakdown at high pH for adducts of thioacetic acid and of *p*-nitrobenzenethiol with acetaldehyde were determined by a "pH-jump" technique in which an equilibrium mixture of aldehyde, thiol, and adduct is perturbed by raising the pH abruptly. This causes most of the adduct to break down to thiol and aldehyde. In one syringe is placed the thiol, acetaldehyde, and the acidic form of the buffer to be used. In the other syringe is placed the basic form of the buffer and acetaldehyde. The acetaldehyde used in pH-jump experiments contained less than 0.05% acid and the final buffer concentration was no greater than 5×10^{-3} *M*. For these conditions buffer catalysis is less than 10%. Since it was possible to measure accurately absorbance changes of ca. 0.05, it was possible to measure half-lives on the order of 0.7 msec by fixing the reaction conditions so that the total absorbance change would be about one absorbance unit. Hence after the 4-5 half-lives required to reach the viewing chamber there is still an absorbance change of 0.03-0.06. The reproducibility for reactions with half-lives of less than 1.5 msec was 10-15%. For the slower reactions it was about 5%.

The activation parameters for the breakdown of the hemithioacetal of thioacetic acid and acetaldehyde were determined by rate measurements at 2, 25, 30, and 40° using the pH-jump technique. The pH values of the reaction mixtures were determined at the reaction temperature.

The kinetic isotope effect in deuterium oxide was determined using the pH-jump technique. The deuterium ion activity was determined with a glass electrode, adding 0.40 to the observed pH meter reading.⁵ It was verified by use of deuteriochloric acid that this correction is valid. Deuterioxide activity was determined by using $pK_w(D_2O) = 14.869$ at 25° .⁶

Product Analysis. By analogy with known reactions of aldehydes and thiols to give hemithioacetals,^{7,8} the products of the reaction studied in this work should be hemithioacetals. Lienhard and Jencks² have shown that the reaction product of several aldehydes and thiols in water is consistent only with the adducts being composed of one molecule of thiol and one of aldehyde. There is spectrophotometric evidence that the adduct of thioacetic acid and acetaldehyde is the expected hemithioacetal, which is also a thio ester. It was found that the adduct has an absorption maximum at 230 $m\mu$ (ϵ 4010). For comparison, ethyl thioacetate has an absorption maximum at 232 $m\mu$ (ϵ 4400).⁹ The absorption maximum of the adduct of benzenethiol and acetaldehyde occurs at 247 $m\mu$ (ϵ ca. 5200). This may be compared with the absorption

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(6) A. K. Covington, R. A. Robinson, and R. G. Bates, *J. Phys. Chem.*, **70**, 3820 (1966).

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(9) R. K. Chaturvedi, A. E. MacMahon, and G. L. Schmir, *J. Amer. Chem. Soc.*, **89**, 6984 (1967).

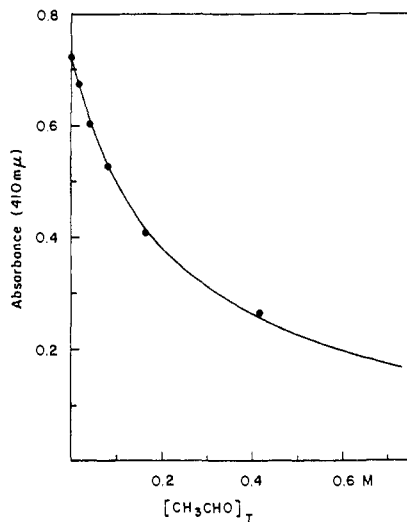


Figure 1. Absorption at equilibrium for mixtures of *p*-nitrobenzenethiol and acetaldehyde at 25°, ionic strength 1.0 *M*, pH 4.29, 0.02 *M* acetate buffer, with 1.44×10^{-4} *M* total thiol initially. Curve calculated for $K_{app} = 4.48$.

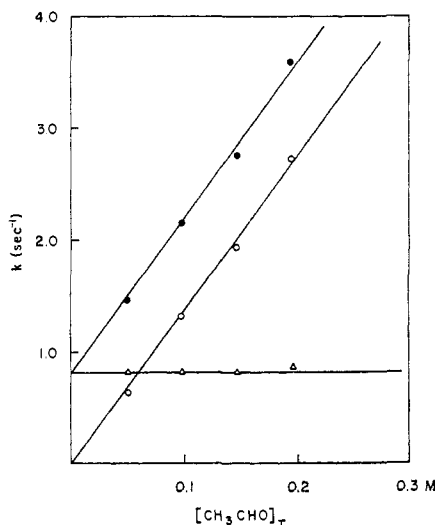


Figure 2. Rate constants for the formation and breakdown of the hemithioacetal formed from acetaldehyde and thioacetic acid at pH 3.07, 0.10 *M* methoxyacetate buffer, 25°, ionic strength 1.0 *M*. Approach to equilibrium, k_{eq} (●); formation, k_f (○); and breakdown, k_b (△).

maximum of the hemithioacetal of benzenethiol and pivaldehyde at 245 $m\mu$ (ϵ ca. 4900).²

Results

Equilibrium Constants. The results of measurements at equilibrium for the reaction of *p*-nitrobenzenethiol and acetaldehyde at pH 4.29 in which the initial thiol concentration was held constant and the aldehyde concentration was varied are shown in Figure 1. The solid line is calculated from a value of $K_{app} = 4.48$ (eq 1). Similar results were obtained for the other two thiols. The equilibrium constant, $K = [\text{hemithioacetal}]/[\text{thiol}][\text{unhydrated aldehyde}]$, was determined from eq 5, in which $K_{hyd} = [\text{hydrated aldehyde}]/[\text{unhydrated aldehyde}]$ and K_{RSH} is the ionization constant of the

$$K = K_{app}(1 + K_{hyd})(1 + K_{RSH}/a_{H^+}) \quad (5)$$

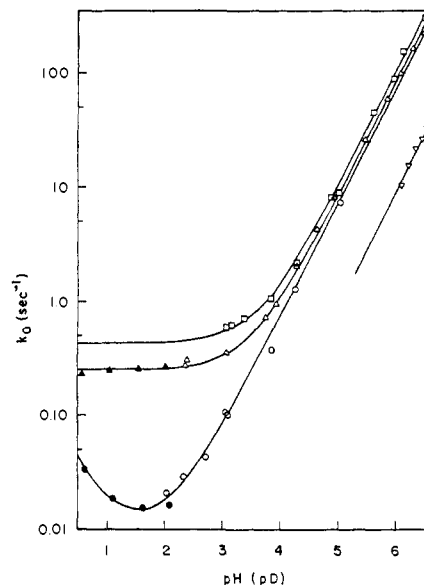


Figure 3. Rates of hemithioacetal breakdown at 25° and ionic strength 1.0 *M*. Hemithioacetals of acetaldehyde and thioacetic acid (triangles), benzenethiol (circles), and *p*-nitrobenzenethiol (squares): open symbols, extrapolated to zero buffer concentration; closed symbols, in dilute hydrochloric acid; inverted triangles, in deuterium oxide solution, 0.005 *M* phosphate buffer.

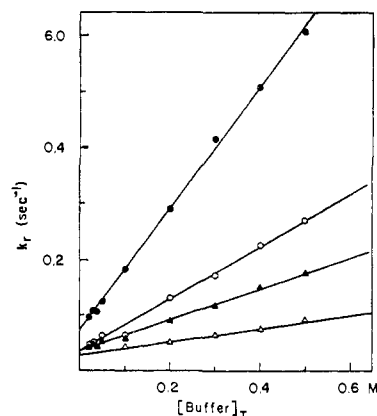


Figure 4. General base catalysis of the decomposition of the hemithioacetal of thioacetic acid and acetaldehyde at 25° and ionic strength 1.0 *M*. Buffers: methoxyacetate (pH 3.78, 70% base), ●; methoxyacetate (pH 3.07, 30% base), ○; chloroacetate (pH 3.09, 70% base), ▲; and chloroacetate (pH 2.37, 30% base), △.

thiol. At an ionic strength of 1.0 *M* $K_{hyd} = 0.85$ for acetaldehyde.² The results are shown in Table I.

Table I. Equilibrium Constants for Hemithioacetal Formation from Acetaldehyde at 25°, Ionic Strength 1.0 *M*

Thiol	pK _a	No. of runs	K, M ⁻¹
Thioacetic acid	3.20	18	55
<i>p</i> -Nitrobenzenethiol	4.57 ^a	10	13 ^b
Benzenethiol	6.33 ^c	6	54 ^d
Methyl mercaptoacetate ^e	7.83		60
2-Methoxyethanethiol ^e	9.50		32
Ethanethiol ^e	10.25		36

^a In 2% ethanol. ^b In 6% ethanol. ^c In 0.5% ethanol. ^d In 1% ethanol. ^e Reference 2.

Table II. Base-Catalyzed Breakdown of the Hemithioacetal of Thioacetic Acid and Acetaldehyde at 25°, Ionic Strength 1.0 M

Base	pK _a ^a	Total buffer, M	% base	pH(D)	No. of runs	k _B , M ⁻¹ sec ⁻¹
Hydroxide	15.74			3.76–6.55	14	8.3 × 10 ⁹
Deuterioxide	16.41 ^b			6.11–6.55	5	6.6 × 10 ⁹
Phosphate monoanion	1.89	0.1–0.5	90	2.88	5	2.09 ^c
		0.1–0.5	70	2.24	5	
Cyanoacetate	2.39	0.092–0.46	97.2	3.92	5	2.11
		0.092–0.46	50	2.39	5	
Chloroacetate	2.72	0.02–0.5	70	3.09	9	4.11
		0.1–0.5	30	2.37	5	
Methoxyacetate	3.44	0.02–0.5	70	3.79	9	1.56 × 10
		0.02–0.5	30	3.04	9	
Acetate	4.64	0.02–0.5	70	5.01	9	1.39 × 10 ²
		0.02–0.5	30	4.26	9	
Phosphate dianion	6.55	0.1–0.5	3.38	5.12 ^d	5	8.9 × 10 ³
		0.1–0.5	0.28	4.00 ^e	5	
Water	–1.74	55.5		0.57–3.10	8	4.58 × 10 ⁻³

^a Except for hydroxide, deuterioxide, and water, the pK_a values were determined from the pH of buffers of known composition. ^b Reference 6. ^c Corrected for catalysis by phosphate dianion. ^d pH controlled with 0.020 M acetate buffer. ^e pH controlled with 0.008 M methoxyacetate buffer.

Table III. Base-Catalyzed Breakdown of the Hemithioacetal of *p*-Nitrobenzenethiol and Acetaldehyde at 25.0°, Ionic Strength 1.0 M, 5% Ethanol

Base	Total buffer, M	% free base	pH	No. of runs	k _B , M ⁻¹ sec ⁻¹
Hydroxide			4.89–6.54	6	9.5 × 10 ⁹
Cyanoacetate	0.037–0.18	90	3.39	5	1.19 × 10
Chloroacetate	0.02–0.10	70	3.10	5	2.04 × 10
Methoxyacetate	0.02–0.10	30	3.15	5	8.29 × 10
	0.02–0.10	70	3.86	5	
Acetate	0.02–0.10	30	4.30	5	5.87 × 10 ²
	0.01–0.05	70	5.05	5	
Water			3.09–4.29	5	7.7 × 10 ⁻³

Table IV. Base-Catalyzed Breakdown of the Hemithioacetal of Benzenethiol and Acetaldehyde at 25.0°, Ionic Strength 1.0 M, 1% Ethanol

Base	Total buffer, M	% free base	pH	No. of runs	k _B , M ⁻¹ sec ⁻¹
Hydroxide			2.73–5.03	6	6.78 × 10 ⁹
Cyanoacetate	0.097–0.48	30	2.01	5	2.0 × 10 ⁻¹
	0.097–0.48	70	2.73	5	
Chloroacetate	0.1–0.5	70	3.10	5	4.09 × 10 ⁻¹
	0.1–0.5	30	2.32	5	
Methoxyacetate	0.1–0.5	30	3.08	5	1.79
	0.1–0.5	70	3.84	5	
Acetate	0.1–0.5	70	5.03	5	1.79 × 10
	0.1–0.5	30	4.25	5	
Water			0.64–2.32	6	1.88 × 10 ⁻⁴

Kinetics of Hemithioacetal Formation and Breakdown.

The rate constants for the breakdown of the hemithioacetal, k_r , were obtained from the observed rate constants, k_{obsd} , for approach to equilibrium. Since the aldehyde is in great excess, the reaction is pseudo first order, and so

$$k_{\text{obsd}} = k_r + k_f \quad (6)$$

where k_f is the pseudo-first-order rate constant for hemithioacetal formation. Since

$$K_{\text{app}}[\text{total aldehyde}] = K_{\text{obsd}} = k_f/k_r \quad (7)$$

it follows that

$$k_r = k_{\text{obsd}}/(1 + K_{\text{obsd}}) \quad (8)$$

Since the reactions are general base catalyzed the value of k_r must be extrapolated to zero buffer concentration to obtain k_0 . The pseudo-first-order rate constants for hemithioacetal formation show the expected direct proportionality to the aldehyde concentration while the

first-order rate constant for hemithioacetal breakdown is independent of aldehyde concentration (Figure 2). The dependence on pH of the first-order rate constants, k_0 , for the breakdown of the hemithioacetals of thioacetic acid, benzenethiol, and *p*-nitrobenzenethiol is shown in Figure 3.

The rate law for the breakdown of these hemithioacetals is shown in eq 9. The effects of methoxyace-

$$k_r = k_{\text{H}_2\text{O}} + k_{\text{OH}^-}[\text{OH}^-] + k_{\text{B}}[\text{B}] \quad (9)$$

tate and chloroacetate buffers on the rate of breakdown of the hemithioacetal of thioacetic acid and acetaldehyde are shown in Figure 4. The breakdown of the hemithioacetal of benzenethiol and acetaldehyde shows an acid-catalyzed term with k_{H^+} equal to approximately 0.10 M⁻¹ sec⁻¹ (Figure 3). The rate constants for the solvent and buffer-catalyzed breakdown of the three hemithioacetals are summarized in Tables II–V. For all three hemithioacetals the rate constants for hydroxide ion catalyzed breakdown are near 10¹⁰ M⁻¹ sec⁻¹. The

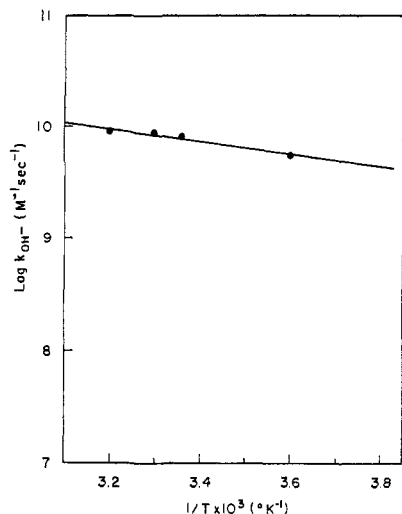


Figure 5. Arrhenius plot for the hydroxide-catalyzed breakdown of the hemithioacetal of acetaldehyde and thioacetic acid, ionic strength 1.0 *M*.

rate constants for catalysis by phosphate monoanion of the breakdown of the hemithioacetal of thioacetic acid and acetaldehyde were corrected for catalysis by the small amount of phosphate dianion present. At pH 2.88 the correction amounted to about 50%; at pH 2.24 the correction was about 25%.

Table V. Breakdown of Hemithioacetals of Acetaldehyde and Various Thiols at 25°, Ionic Strength 1.0 *M*

Thiol	pK _a	k _{H₂O} , sec ⁻¹	k _{OH⁻} × 10 ⁻¹⁰ , M ⁻¹ sec ⁻¹	
			Obsd	Calcd ^b
Thioacetic acid	3.20	0.25	0.83 0.98 ^c	0.83
<i>p</i> -Nitrobenzenethiol	4.57 ^d	0.43 ^e	0.95 ^e	0.89
Benzenethiol	6.33 ^f	0.010 ^g	0.68 ^g	0.69

^a Based on hydroxide ion activity. ^b See text. ^c Ionic strength 0.003–0.010 *M*. ^d In 2% ethanol. ^e In 5% ethanol. ^f In 0.5% ethanol. ^g In 1% ethanol.

The Arrhenius plot for the determination of the activation parameters for the hydroxide-catalyzed breakdown of the hemithioacetal of thioacetic acid and acetaldehyde between 2 and 40° is shown in Figure 5. The calculated activation parameters are $E_a = 2.5 \pm 0.5$ kcal/mole, $\Delta H^{\ddagger}_{298} = 1.9 \pm 0.5$ kcal/mole, and $\Delta S^{\ddagger} = -7 \pm 2$ eu.

Isotope Effects. The observed rate of breakdown of the hemithioacetal of thioacetic acid and acetaldehyde is 9.25 times slower in deuterium oxide than in water at a given high pH (pD) value. This decrease is largely a consequence of the isotope effect on the ionization of deuterium oxide and the isotope effect on the hydroxide (deuterioxide) catalyzed breakdown of the hemithioacetal, k_{OH^-}/k_{OD^-} , is 1.25 ± 0.14 .

Discussion

Equilibrium Constants. It was observed by Lienhard and Jencks² that the equilibrium constants for the formation of hemithioacetals of acetaldehyde and various aliphatic thiols are not sensitive to the ionization constant of the thiols, with only a twofold variation in the

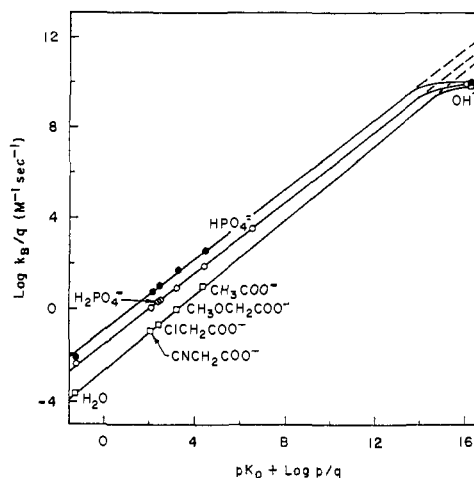


Figure 6. Brønsted plots for hemithioacetal breakdown at 25° and ionic strength 1.0 *M* for the hemithioacetals of acetaldehyde and thioacetic acid (○), *p*-nitrobenzenethiol (●), and benzenethiol (□). Statistical corrections have been made according to R. P. Bell and P. G. Evans, *Proc. Roy. Soc. (London)*, **A291**, 297 (1966).

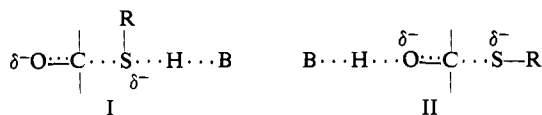
equilibrium constant for thiols with ionization constants varying by 100. This observation has been extended to show that there is less than a fivefold variation in the equilibrium constants for thiols with ionization constants varying by 10⁷ (Table I). A similar insensitivity to polar effects has been observed for the addition of carbon acids and simple amines to the carbonyl group and may be explained by the similar polar effects of hydrogen and the -CHROH group, so that polar substituents do not have different effects on the stability of starting materials and products.¹⁰ In the oxygen series, however, the reduced affinity of acidic compounds such as trifluoroethanol and acetic acid toward the carbonyl group has been ascribed to a stabilization of the acid by hydrogen bonding to the solvent, which is lost upon hemiacetal formation.^{10d} According to this interpretation, the insensitivity to acidity of the affinity of thiols toward the carbonyl group suggests that the -SH group, like the -CH and -NH groups, is not very much stabilized by hydrogen bonding to the solvent.

General Base Catalysis. The formation and breakdown of hemithioacetals of weakly acidic thiols and acetaldehyde are not subject to observable general base catalysis.² General base catalysis does occur for the decomposition of hemithioacetals of acidic thiols (Figure 4, Tables II–IV). For hemithioacetals of thioacetic acid, *p*-nitrobenzenethiol, and benzenethiol with acetaldehyde the Brønsted coefficient β for general base catalysis is 0.80 ± 0.03 (Figure 6). There is a small increase in slope for the less reactive compounds, but the increase is not certainly larger than the experimental error. The rate constants for catalysis by phosphate monoanion and phosphate dianion do not deviate from the Brønsted plot determined by the rate constants for four carboxylate anions for catalysis of the breakdown of the hemithioacetal of thioacetic acid and acetaldehyde, so bifunctional catalysis is not important for this reaction. The rate constants for catalysis by water, ob-

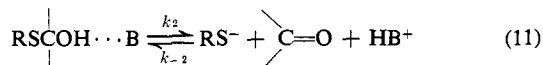
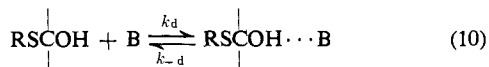
(10) (a) T. N. Hall, *J. Org. Chem.*, **29**, 3587 (1964); (b) J. Hine and R. D. Weimar, Jr., *J. Amer. Chem. Soc.*, **87**, 3387 (1965); (c) R. G. Kalten and W. P. Jencks, *J. Biol. Chem.* **241**, 5864 (1966); (d) E. G. Sander and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 6154 (1968).

tained by dividing the pH-independent pseudo-first-order rate constants for hemithioacetal decomposition by the concentration of water (55.5 *M*), deviate little or not at all from the Brønsted plots for all three hemithioacetals. Thus, the pH-independent breakdown presumably represents general base catalysis by water. Above pH 4 the rate of hemithioacetal breakdown is proportional to hydroxide ion activity. The rate constants for catalysis by hydroxide ion are very similar for the three hemithioacetals and are all near $10^{10} M^{-1} \text{sec}^{-1}$ (Table V). These rate constants fall low on the Brønsted plots (Figure 6).

Two possible mechanisms for the general base catalyzed breakdown of hemithioacetals are illustrated by transition states I and II. Mechanism I corresponds to the rapid formation of the hemithioacetal anion in a preequilibrium step, followed by general acid catalysis of the expulsion of thiol. In the direction of hemithioacetal formation, it corresponds to general base catalysis by removal of a proton from the attacking thiol. Mechanism II corresponds to general base catalysis of the elimination of thiol anion and, in the reverse direction, to general acid catalysis of the addition of thiol anion by proton donation to the carbonyl group. The mechanism of transition state I can be ruled out if one considers the process from the direction of hemithio-



acetal formation. Catalysis is observed at pH 5 for the thioacetic acid-acetaldehyde reaction. At this pH the thiol is already more than 98% ionized to the anion, so that catalysis by partial proton removal from the small amount of free thiol present could hardly give rise to a significant rate increase. The observed catalysis in the presence of 0.5 *M* acetate at this pH corresponds to a rate increase of more than eightfold. With hydroxide ion as the catalyzing base the third-order rate constant required for hemithioacetal formation according to mechanism I is $4.6 \times 10^{11} M^{-2} \text{sec}^{-1}$. This is greater than the second-order rate constant for a diffusion-controlled reaction,¹¹ and it does not appear possible to divide this reaction into a series of bimolecular reactions which would proceed at less than diffusion-controlled rates. This leaves the mechanism of transition state II, as shown in eq 10–12, as the most prob-



able mechanism. If the Brønsted plots for the three hemithioacetals are extrapolated to the $\text{p}K_a$ of hydroxide ion (15.74), the rate constants predicted for hydroxide ion catalysis are in excess of $10^{10} M^{-1} \text{sec}^{-1}$, the rate constant expected for a diffusion-controlled reaction. This implies that if the mechanism of eq 10–12 is correct catalysis by hydroxide ion should be diffusion controlled and the rate constants should be near $10^{10} M^{-1} \text{sec}^{-1}$.

(11) M. Eigen, *Angew. Chem. Intern. Ed. Engl.*, **3**, 1 (1964).

The rate constant for the diffusion-controlled reaction of hydroxide ion with the hemithioacetal of thioacetic acid and acetaldehyde was estimated from eq 13, in which k is the rate constant in $M^{-1} \text{sec}^{-1}$, ρ_{AB} the reaction distance in centimeters, D_{AB} the sum of the diffusion coefficients of the reacting species, and N is Avogadro's number.¹² The reaction distance was taken as the sum of the van der Waals radii of the hydrogen

$$k = 4\pi\rho_{AB}D_{AB}N/1000 \quad (13)$$

and oxygen atoms, 1.2×10^{-8} and 1.4×10^{-8} cm, respectively,¹³ giving a value of 2.6×10^{-8} cm. A diffusion coefficient, $D_0 = 5.28 \times 10^{-5} \text{cm}^2 \text{sec}^{-1}$, for hydroxide ion at 25° was obtained from its equivalent conductance, $\lambda^0 = 197.8 \text{mho cm}^2/\text{g equiv}$ according to eq 14.^{14,15} The molecular weight of the hemithio-

$$D_0 = 8.936 \times 10^{-10} T \lambda^0 / [z] \quad (14)$$

acetal of thioacetic acid and acetaldehyde is close to that of *p*-aminobenzoic acid, which has a diffusion coefficient¹⁶ at 25° of $8.42 \times 10^{-6} \text{cm}^2 \text{sec}^{-1}$. Thus D_{AB} is $6.12 \times 10^{-5} \text{cm}^2 \text{sec}^{-1}$. Substitution of these values into eq 13 gives a value of $1.2 \times 10^{10} M^{-1} \text{sec}^{-1}$ for the diffusion-limited rate constant. The observed value at ionic strength 1.0 *M* is $0.83 \times 10^{10} M^{-1} \text{sec}^{-1}$ for the hydroxide ion catalyzed breakdown of the hemithioacetal of thioacetic acid and acetaldehyde. The agreement is adequate. However, the observed rate constant is based on hydroxide ion activity at ionic strength 1.0 *M*, while the calculation is based on concentrations at zero ionic strength. The error introduced by using activities is not large because at ionic strength 0.003–0.010 *M* the observed rate constant is $0.98 \times 10^{10} M^{-1} \text{sec}^{-1}$ (Table V). By way of comparison, the rate constants¹¹ for the reaction of hydroxide ion with phenol ($\text{p}K_a = 9.98$), glycine ($\text{p}K_a = 9.78$), and uracil ($\text{p}K_a = 9.45$) are 1.4×10^{10} , 1.4×10^{10} , and 0.98×10^{10} .

Catalysis by bases weaker than hydroxide ion is not diffusion controlled for the reaction in either direction, because the observed rate constants are much less than those for a diffusion-controlled reaction and the value of β for these compounds is not 1.0. If the reaction in the reverse direction (*i.e.*, the protonation of a hemithioacetal anion) were diffusion controlled, the β value for the removal of a proton from the free hemithioacetal by weak bases would be 1.0, the value expected for a thermodynamically unfavorable proton-transfer reaction.¹¹

Calculations based on the steady-state rate equation (eq 15) for the mechanism of eq 10–12, using values of $k_d k_2 / k_{-2}$ from the Brønsted plots and the assumption

$$k_B = k_d k_2 / (k_{-d} + k_2) \quad (15)$$

that $k_d = 0.9 \times 10^{10} M^{-1} \text{sec}^{-1}$, suggest that diffusion-controlled encounter is largely rate limiting for the

(12) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, John Wiley & Sons, Inc., New York, N. Y., 1961, p 271.

(13) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, N. Y., 1959, p 51.

(14) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1958, p 244.

(15) V. Sivertz, R. E. Reitmeier, and H. V. Tartar, *J. Amer. Chem. Soc.*, **62**, 1379 (1940).

(16) S. B. Tuwiner, "Diffusion and Membrane Techniques," Reinhold Publishing Corp., New York, N. Y., 1962, p 100.

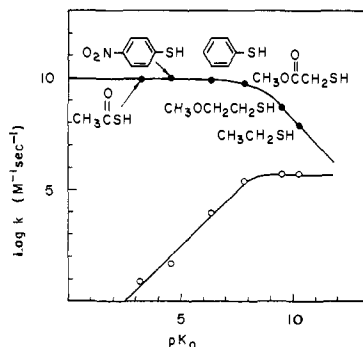


Figure 7. Rate constants for the formation and decomposition of hemithioacetals of acetaldehyde at 25° and ionic strength 1.0 *M*: closed circles, for hydroxide ion catalyzed hemithioacetal cleavage; open circles, for reaction of thiol anion with acetaldehyde.

breakdown of the hemithioacetals of thioacetic acid and *p*-nitrobenzenethiol, whereas the slower rate constant of $0.68 \times 10^{10} \text{ M}^{-1} \text{ sec}^{-1}$ for the hemithioacetal of benzenethiol suggests that both the k_d and k_2 steps contribute to the observed rate (Table V). This latter result is not unexpected, because benzenethiol is the least acidic thiol examined and for weakly acidic thiols the expulsion of the thiol anion from the hemithioacetal is largely or entirely rate limiting.²

The Arrhenius energy of activation for the hydroxide ion catalyzed breakdown of the hemithioacetal of thioacetic acid and acetaldehyde is in the range of 2–3 kcal/mole, while the enthalpy of activation at 25° is in the range of 1.5–2.5 kcal/mole. These values are somewhat lower than Logan's calculated activation energies of 2.5–4.5 kcal/mole for diffusion-controlled reactions.¹⁷ However, they are in the same range as those observed for the reaction of the hydrated proton and hydroxide ion with water¹⁸ and for the reaction of the hydrated electron with the hydrated proton,¹⁹ and are higher than the activation energies near zero for the reaction of ammonia with ammonium ion or the hydrated proton.²⁰

If the hydroxide ion catalyzed breakdown of the hemithioacetal of thioacetic acid and acetaldehyde is diffusion controlled, the deuterium isotope effect on the reaction should be solely a solvent effect on the diffusion coefficients of the species involved. The reaction of the hydrated proton with trimethylamine is 1.3 times slower in deuterium oxide.²¹ The diffusion coefficient for the hydrated proton is 1.47 times smaller in deuterium oxide, while the diffusion coefficients for potassium ion and chloride ion are 1.18 times smaller in deuterium oxide.²² The hydroxide ion catalyzed breakdown of the hemithioacetal of thioacetic acid and acetaldehyde has a rate constant that is 1.25 times smaller in deuterium oxide. This is in the range expected for a diffusion-limited process.

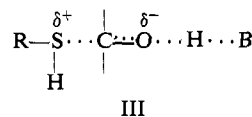
General Mechanistic Considerations. In the mechanism of eq 10–12 for the breakdown of hemithioacetals of acetaldehyde, the step of eq 10 is rate determining for the hydroxide ion catalyzed breakdown of hemithioacetals of acidic thiols. The step of eq 11 is rate de-

termining for catalysis by weaker bases and for hemithioacetals of weakly acidic thiols. For weakly acidic thiols the Brønsted coefficient must be near 1.0, since no general base catalysis has been observed.² An increase in β with decreasing leaving ability (*i.e.*, decreased acidity) is expected from quantitative structure–reactivity correlations.^{23,24} The pertinent equation for the reaction of thiols with acetaldehyde is shown in eq 16, in which n_k is the nucleophilicity of the attacking nucleophile, α_k and α_0 are the Brønsted coefficients for the general acid catalyzed attack of the nucleophile in observed and reference reactions, respectively, and c_2 is a positive constant. In the direction of hemithio-

$$n_k = c_2(\alpha_0 - \alpha_k) \quad (16)$$

acetal formation the mechanism of eq 11 corresponds to general acid catalyzed attack of the thiol anion, for which $\alpha = 1 - \beta$. An increase in the basicity of the thiol anion might be expected to result in a decrease in α for general acid catalyzed attack of the thiol anion and an increase in β for base-catalyzed decomposition of the hemithioacetal. For sufficiently basic thiols one would expect β to approach 1.0 so that no general base catalysis would be observed. This result provides further support for mechanism II, as opposed to mechanism I, because β would be expected to change in the opposite direction with changing basicity of the thiol for mechanism I. It is also in accord with the behavior observed for the reactions of other nucleophiles with carbonyl compounds, which exhibit no general acid catalysis (*i.e.*, $\alpha = 0$) for the attack of strongly basic nucleophiles, such as basic thiol anions, and significant general acid catalysis for more weakly basic nucleophiles, such as thiol anions (for which $\alpha = 0.2$).²⁵

For attack of the free thiol, which is a still weaker base and nucleophile, there exists a general acid catalyzed pathway with a large value of α .² This pathway is significant for basic thiols and probably accounts for the acid catalysis of benzenethiol addition to acetaldehyde (Figure 3). The probable mechanism for the rate-determining step of this reaction is shown in transition state III.



In Figure 7 are plotted the rate constants for hydroxide ion catalyzed hemithioacetal breakdown (upper line) and for the attack of thiol anion on acetaldehyde (lower line) as a function of the pK of the departing or attacking thiol. There is a break in this structure–reactivity correlation at thiols of $pK = 8$. For hemithioacetal breakdown this corresponds to a transition from rate-determining thiolate expulsion for the basic thiolate anions, which exhibits a Brønsted slope β of 1.0 with respect to the pK of the thiol, to rate-determining diffusion-controlled encounter of hemithioacetal with hydroxide ion for less basic thiolates, which exhibits the β value of 0 expected for a diffusion-limited reaction. The rate of attack of basic thiolates on acetal-

(17) S. R. Logan, *Trans. Faraday Soc.*, **63**, 1712 (1967).
 (18) R. E. Glick and K. C. Tewari, *J. Chem. Phys.*, **44**, 546 (1966).
 (19) B. Cercek and M. Ebert, *J. Phys. Chem.*, **72**, 766 (1968).
 (20) Z. Luz and S. Meiboom, *J. Amer. Chem. Soc.*, **86**, 4768 (1964).
 (21) R. J. Day and C. N. Reilly, *J. Phys. Chem.*, **71**, 1588 (1967).
 (22) G. N. Lewis and T. C. Doody, *J. Amer. Chem. Soc.*, **55**, 3504 (1933).

(23) E. H. Cordes and W. P. Jencks, *ibid.*, **84**, 4319 (1962).
 (24) L. do Amaral, W. A. Sandstrom, and E. H. Cordes, *ibid.*, **88**, 2225 (1966).
 (25) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill Book Co., New York, N. Y., 1969, p 193–198.

dehyde is insensitive to the pK of the thiol ($\beta = 0$) as reported previously.² A possible explanation for this insensitivity is that there is back-bonding of electrons on the carbonyl group to sulfur d orbitals in the transition state. The rate constants for attack of less basic thiol anions display a large sensitivity to their basicity ($\beta = 1.0$), which corresponds to the β value of 0 for the reverse reaction and the insensitivity of the equilibrium to basicity.

Since diffusion-controlled encounter of hydroxide ion and hemithioacetal is rate determining for the decomposition reaction, it follows from the principle of microscopic reversibility that the separation of hydroxide ion from the neutral hemithioacetal is rate determining in the direction of synthesis for these compounds. In other words, the addition of thiol anion and proton transfer from water to the carbonyl oxygen atom occur in a rapid, reversible reaction (eq 11), and the final product is formed only when the hydroxide ion produced as a result of this proton donation diffuses away from the hemithioacetal (eq 10). The important point in this reaction is that cleavage of the carbon-sulfur bond and proton transfer within the solvent "cage" (k_2 of eq 11) are faster than the separation of hydroxide ion from the hemithioacetal (k_{-d} of eq 10). Under these circumstances there is no formation or breaking of bonds to carbon or proton transfer in the rate-determining step of the reaction in either direction although the observed rate constant for hemithioacetal synthesis is small.

A somewhat similar situation is observed in the intramolecular attack of amine on a thiol ester to give a dipolar product which reverts to starting materials unless it is trapped by diffusion-controlled encounter with an acid to protonate the oxygen atom.²⁶ In both of these reactions a relatively slow observed rate constant can

(26) R. Barnett and W. P. Jencks, *J. Amer. Chem. Soc.*, **90**, 4199 (1968); **91**, 2358 (1969).

reflect a rate-determining diffusion-controlled encounter or separation of catalyst molecules, which is preceded by a rapid unfavorable equilibrium step in which bond formation to carbon takes place. Evidence for a similar rate-determining diffusion-controlled step has been observed in the breakdown of acyclic thioimidates to the corresponding thiol esters.²⁷

An important mechanistic conclusion follows from the observation that the rate constants for the breakdown of hemithioacetals catalyzed by bases weaker than hydroxide ion are much less than diffusion controlled and follow a Brønsted slope of 0.8 (Figure 6). This result indicates that the proton transfer in these reactions does not occur in a separate step that requires diffusion together of the reactants and catalyzing base; *i.e.*, the reaction is, in some sense, "concerted." If the proton transfer and carbon-sulfur cleavage occurred in separate steps, the value of β would be 0 or 1.0.¹¹ The slope of the Brønsted lines of Figure 6 must be equal or close to zero at the diffusion-controlled upper limit so that there must be a rather sharp break in the lines close to this limit in order to connect with the lines of slope 0.8 extrapolated from the observed catalytic coefficients of weaker bases. Since this break must occur close to the diffusion-controlled limit, the observed rate constants require that the remainder of the line be almost linear and that the observed β value of 0.8 does not merely represent a region of curvature of the Brønsted plot for diffusion-controlled proton transfer between the regions in which β equals 0 and 1.0. The β value of 0.8 does not necessarily mean that the proton is not in a potential well in the transition state, but it does suggest that its average position has changed from that in the starting material and that its transfer toward the catalyzing base is well advanced in the transition state at the time that cleavage of the carbon-sulfur bond takes place.

(27) R. K. Chaturvedi and G. L. Schmir, *ibid.*, **91**, 737 (1969).